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2-ALKYLTHIAZOLYL BENZIMIDAZOLES AND α-HALOGEN- OR α-AMINO-2-ALKYLTHIADIAZOLYL BENZIMIDAZOLES

[Thiazolylalcoyl-2 benzimidazoles et thiadiazolylalcoyl-2 benzimidazoles α halogénés ou α-aminés

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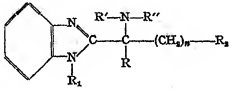
FOREIGN TITLE (54A): THIAZOLYLALCOYL-2 BENZIMIDAZOLES ET THIADIAZOLYLALCOYL-2 BENZIMIDAZOLES α-HALOGÉNÉS OU α-AMINÉS

The present invention concerns products derived from benzimidazole answering to the following general formula: /1*



In this formula:

n can be comprised between 0 and 3 inclusively;

R represents an atom of hydrogen or an alkyl, alkenyl, aralkyl or aryl radical;

R' and R'' can be like or unlike, and each represents an atom of hydrogen or an alkyl, alkenyl, aralkyl, aralkenyl, aryl or cyclanyl radical; the R'-N-R'' group can also be replaced by an azotized heterocycle attached by one or more of its hydrogen atoms;

R_1 represents an alkyl, alkenyl, aralkyl, aralkenyl or aryl radical, or an atom of hydrogen;

R_2 represents a five-element heterocycle with an atom of sulfur and one or more nitrogen atoms attached by one or more of its carbon atoms; this heterocycle carries, on one or more of its carbon atoms, one or more alkyl, alkenyl, aralkyl, aralkenyl and/or aryl radicals. The benzene nucleus of the benzimidazole carries one or more hydrogen atoms and/or one or more halides and/or one or more nitro groups and/or one or more alkyl, alkenyl, aralkyl, aralkenyl and/or aryl radicals bonded to the core directly or via an intermediary atom of sulfur or oxygen.

*Numbers in the margin indicate pagination in the foreign text.

Likewise foreseen by the invention are those products defined above in which the group R'-N-R'' is replaced by a halogen.

Likewise foreseen by the invention are those salts formed between said products and mineral or organic acids. As mineral acids, it is possible to cite, as nonlimitative examples, halohydric, sulfuric, phosphoric, boric or nitric acids; as organic acids, it is possible to cite, likewise as nonlimitative examples, mono- or polycarboxylic or polysulfonic acids. The organic acids can carry attached functions represented by one or more of the halogens and/or one or more of the groups hydroxy, alkoxy, nitro, amino, alkylamino and/or acylamino.

The invention likewise concerns those salts formed between the above-defined products and the phenols or mercaptans.

The invention furthermore provides for the nonpharmaceutical use of the products, in the salt state or not, as agents for combating the following live harmful organisms:

The parasitic helminths of animals and man;

The parasitic fungi of animals and man;

The saprophytes and saprozoites in general;

The parasitic viruses of animals and man;

The pathogenic viruses of vegetables;

The pathogenic bacteria.

The products according to the invention can be employed alone or in combinations of two or more; they can also be employed in the form of liquid, plastic or solid compositions.

A composition can be constituted by one or more products of the invention, either alone or in a mixture with one or more inert

products and/or one or more product possessing one or more activities similar or foreign to those forming the object of the invention.

A liquid composition can, for example, be a solution or a /2
suspension or a dispersion in water or in any suitable liquid.

A solid composition can, for example, be presented in the form of powder, granules, compressed tablets, agglomerates or doses containing one or more of these forms.

A plastic composition can, for example, be a solution or a suspension or a dispersion in a plastic substance such as a more or less compact fat or a liquid with elevated viscosity in order to constitute, for example, a liniment, a pomade, a cream, a balm, an unguent or a plaster.

The compositions can be employed, for example, for sprinkling, spraying, irrigation, lavage, nebulization, vaporization or fumigation effected manually or by instrumental methods, motorized or not.

In the case of internal therapy, the compositions can be employed by ingestion or injection or according to any other mode of penetration.

As nonlimitative examples, it is possible to cite the following compositions:

A food or alimentary premixture containing one or more products of the invention, all being designed for the alimentation of domestic animals and at the same time for the prevention of infectious diseases in the latter;

A fertilizer, composite or not, containing one or more of the products of the invention destined for the disinfection of the soil and the treatment or protection of plants by systematic action.

The α-halogen compounds according to the invention are prepared by the action of halogenating agents upon appropriately substituted α-hydroxylated benzimidazoles. As halogenating agents it is possible to cite, for example, the halohydric acids in the presence or not of a dehydrating agent, the phosphorus and thionyl halides. The operation can be carried out in a solvent or inert support liquid, in which case the halogenating agent, utilized in excess or not, can constitute all or part of the solvent or support. The ambient temperature can be sufficient, but it is often useful to apply heat in order to improve and/or finish the reaction.

The α-amino compounds according to the invention are prepared by the action of ammoniac or amines or heterocycles possessing an -NH- chain upon suitably substituted α-halogen benzimidazoles. The reaction is carried out, by preference, in an inert liquid serving as a solvent or support, such as, for example, the alcohols, hydrocarbides, ether-oxides and/or oxygenated heterocycles. The ambient temperature can often suffice, but a higher temperature is generally preferable, for example, the reflux temperature of the solvent or support. The presence of an acid acceptor, such as, for example, a mineral base or a tertiary amine, favors the reaction by fixing the halohydric acid formed. This acceptor can be all or part of the solvent or support and/or be constituted by an excess of the amine reacted. The operation can be carried out under atmospheric pressure or under a different pressure, a higher pressure having the power to reduce the duration of the operation and/or increase the yield. In the absence of acid acceptor, the benzimidazole functions as such and the product formed is a halohydrate.

The salts of the invention can be obtained for example, from products of the invention in the state of free based, by the action of an acid, a phenol or a mercaptan.

The free bases can be obtained for example, from salts of the invention, by the action of a strong base.

Some preparation examples are given below; these examples are purely illustrative and by no means limitative of the invention.

1. 1-Methyl-(4-thiazolyl)-2-chloromethyl benzimidazole. 24.5 g (0.1 mole) of 1-methyl-(4-thiazolyl)-2-hydroxymethyl benzimidazole in 150 ml of acetonitrile are treated with 5.5 g (0.04 mole) of phosphorus trichloride added little by little while agitating and cooling in a manner that does not exceed 30 °C; the reaction mixture is maintained at ambient temperature for one hour more, the excess phosphorus trichloride and the greater part of the acetonitrile then being distilled under reduced pressure. The residue is then poured into mixture constituted by 50 g of ground ice and 200 ml of water; the product is separated by filtration.

2. 1-Methyl-(4-thiazolyl)-2-chloromethyl benzimidazole. 24.5 g (0.1 mole) of 1-methyl-(4-thiazolyl)-2-hydroxymethyl benzimidazole in 150 ml of chloroform are heated to 25/30 °C; 16.7 g (0.14 mole) of thionyl chloride are then added little by little, with agitation, without exceeding 50 °C. The reaction mixture is then heated for one hour to 60/65 °C, and the excess thionyl chloride and then the chloroform are distilled under reduced pressure. The residue is washed in cold water.

3. *1-Methyl-(4-thiazolyl)-2-bromomethyl benzimidazole.* The procedure is the same as than in Example 1, but with the utilization of 10.8 g (0.04 mole) of phosphorus tribromide.

4. *1-Benzyl-2-[1-chloro-2-(2-phenyl-4-thiazolyl)-ethyl] benzimidazole.* The procedure is the same as than in Examples 1 and 2, but with the utilization of 41.1 g (0.1 mole) of 1-benzyl-2-[1-hydroxy-2 (2-phenyl-4-thiazolyl)-ethyl] benzimidazole.

5. *1-Phenyl-2-[1-chloro-2-(4-thiadiazol-1,2,3-yl)-ethyl] benzimidazole.* The procedure is the same as than in Examples 1 and 2, but with the utilization of 32.2 g (0.1 mole) of 1-phenyl-2-[1-hydroxy-2-(4-thiadiazolyl-1,2,3-yl)-ethyl] benzimidazole;

6. *1-Methyl-(4,5-dimethyl-2-thiazolyl)-2-aminomethyl benzimidazole.* 29.2 g (0.1 mole) of 1-methyl-(4,5-dimethyl-2-thiazolyl)-2-chloromethyl benzimidazole are treated with 300 ml of concentrated ammoniac in an autoclave that is gently heated until the exothermic reaction is triggered, which takes place at between 70 and 90 °C. The heat is then abruptly switched off, and the reaction is /3 allowed to continue by itself. When the temperature begins to drop, the reaction mixture is cooled to ambient temperature, the autoclave is emptied and several extractions are carried out in chloroform. The combined extracts are dried on potassium carbonate, and the chloroform is eliminated by distillation under reduced pressure.

7. *1-Methyl-2-[N,N-1-diethylamino-2-(4-thiazolyl)-ethyl] benzimidazole.* 27.8 grams (0.1 mole) of 1-methyl-2-[1-chloro-2-(4-thiazolyl)-ethyl] benzimidazole in 200 ml of methyl ethyl ketone are treated, while maintaining good agitation, with 15 grams (0.1 mole) of anhydrous sodium iodide. The reaction mixture is heated to reflux for

one hour and filtered to eliminate the sodium chloride formed. 14.6 grams (0.2 mole) of diethylamine are added to the filtrate and brought to reflux for eight hours. The solvent is eliminated by distillation under reduced pressure, and the residue is submitted to an extraction by boiling ethanol and filtered, the ethanol being then eliminated under reduced pressure.

8. 1-Methyl-2-[1-piperidino-2-(4-thiazolyl)-ethyl] benzimidazole. The procedure is the same as that in Example 7, but with the utilization of 17 grams (0.2 mole) of piperidine.

9. 1-Allyl-2-[N,N-1-diethylamino-2-(4-isothiazolyl)-ethyl]-5-nitro benzimidazole. The procedure is the same as that in Example 7, but with the utilization of 39.3 grams (0.1 mole) of 1-allyl-2-[1-bromo-2-(4-isothiazolyl)-ethyl]-5-nitro benzimidazole.

10. 1-Methyl-2-[N-1-morpholino-2-(4-thiazolyl)-ethyl] benzimidazole. The procedure is the same as that in Example 7, but with the utilization of 17.4 grams (0.2 mole) of morpholine.

11. 2-[N,N-2-diethylamino-1-(4-thiazolyl)-2-propyl)-5,6-dichloro benzimidazole. The procedure is the same as that in Example 7, but with the utilization of 39.1 grams (0.1 mole) of 2-[2-bromo-1-(4-thiazolyl)-2-propyl]-5,6-dichloro benzimidazole.

CLAIMS

The invention concerns:

1. As new products, those benzimidazoles possessing the following substitutions:

In position **1**, an atom of hydrogen or an alkyl, alkenyl, aralkyl, aralkenyl or aryl radical;

In position **2**, a hydrocarbon radical containing from one to four carbon atoms in a saturated straight chain that carries, in position one, an alkyl, alkenyl, aralkyl, aralkenyl or aryl group or a halogen or amino group constituted by a nitrogen atom belonging to a heterocycle, or carrying one or two hydrogen atoms or one of them with an alkyl, alkenyl, aralkyl, aralkenyl or cyclanyl group or two of these radicals that are alike or different; the hydrocarbon group carries, at the end of the chain, a five-element heterocycle with a atom of sulfur and a nitrogen atom attached via one of its carbon atoms; its other carbon atom or atoms carry one or more hydrogen atoms and/or one of the radicals from the group constituted by alkyl, alkenyl, aralkyl, aralkenyl and/or aryl;

In any position on the benzene nucleus of the benzimidazole, one or more hydrogen atoms and/or halogens and/or one or more nitro groups, and/or one or more alkyl, alkenyl, aralkyl and/or aryl groups attached to the nucleus directly or via an intermediary atom of sulfur or oxygen.

2. As new products, those salts formed between the compounds defined in Claim 1 and the organic or mineral acids, the phenols or the mercaptans.

3. The nontherapeutic application of those products defined in Claims 1 and 2 as agents for combating the live harmful organisms below:

The parasitic helminths of animals and man;

The parasitic fungi of animals and man;

The saprophytes and saprozoites in general;

The parasitic viruses of animals and man;

The pathogenic viruses of vegetables;

The pathogenic bacteria.

4. Liquid, plastic or solid compositions containing one or more of the products of the invention and destined for the above applications.

5. The manufacture of the products by the action of halogenating agents upon the suitably substituted o-hydroxylated benzimidazoles.

6. The manufacture of the products by the action of ammoniac, the amines or heterocycles possessing an -NH- chain upon the suitably substituted o-hydroxylated benzimidazoles.

7. The manufacture of those salts defined in 2 by the action of acids, phenols or mercaptans upon those products defined in Claim 1.

8. The manufacture of those bases defined Claim 1 by the action of strong bases upon those salts defined in Claim 2.